REMARKS

Claims 31-71 are currently pending in the subject application and have been examined on the merits.

Claims 31-71 have been rejected under 35 U.S.C. § 112, ¶ 1, as purportedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. In other words, claims 31-71 have been rejected as purportedly failing to comply with the enablement requirement.

Applicants respectfully traverse this rejection. Applicants have previously addressed this outstanding enablement rejection with arguments and evidence submitted with Applicants' *Response to Office Action* filed December 16, 2005 and the *Declaration of Katherine C. Faria* ("*Faria Declaration*"). In response to Applicants' arguments and evidence, the Examiner issued a *Final Office Action* of March 28, 2006 ("*Final Office Action*") and stated that Applicants' arguments were not fully persuasive since the scope of the term "culturing conditions" as applied in the outstanding enablement rejection was broader than the testimony provided in the *Faria Declaration*. *Final Office Action*, p. 6. Applicants respectfully disagree and submit that the *Faria Declaration* fully addressed the outstanding enablement rejection. Nevertheless, in the interest of completing the evidentiary record before proceeding to appeal, Applicants thus file this *37 C.F.R. § 1.114 Response To Office Action* and the *Second Declaration Of Katherine C. Faria* ("*Second Faria Declaration*") to address the Examiner's broader "culturing conditions" argument in the *Final Office Action*.

As set forth in the previous response, the presently claimed invention is directed to a multilayered cultured skin construct comprising cultured dermal fibroblast cells that synthesize, assemble and produce a layer of extracellular matrix in the absence of any exogenous matrix components and/or a mesh member acting as a support during the culturing conditions.

The multilayered skin construct also comprises a second layer of epithelial cells disposed on the first layer to form an epidermal cell layer when the selected epithelial cells are keratinocytes.

Applicants submit that one of ordinary skill in the art would be able to, from reading the Specification, prepare without undue experimentation the cultured skin construct of the claimed invention. *Second Faria Declaration*, ¶ 10.

Applicants have previously provided an analysis of the eight *Wands* factors in their December 16, 2005 *Response to Office Action*, which is herein incorporated by reference. Applicants thus further submit the following analysis for *Wands* factors (3-8) with respect to the specific "culturing conditions" argument advanced by the Examiner in the *Final Office Action*:

3. The State Of The Prior Art

"Culturing conditions" is a term of art which include various conditions associated with culturing cells. *Second Faria Declaration,* ¶ 12. Culturing conditions can be intangible/environmental in nature (*e.g.*, temperature, humidity, etc.) or can be more tangible in nature (*e.g.*, specific additives, growth factors, culture media, support structure, etc.). *Second Faria Declaration*, ¶ 13.

Both types of culturing conditions go hand in hand. That is, the intangible/environmental and the tangible culturing conditions used to culture cells are typically taught or disclosed together in the art. Thus, if the culture media for culturing a specific type of cell is known, then all of the other conditions (*i.e.*, support structure, environmental conditions, etc.) would also be known and disclosed in the same art since it is within a scientist's routine practice

to disclose all culturing conditions used to culture the specific cells being researched or experimented on. *Second Faria Declaration,* ¶ 14.

As was previously explained, it is well known what culture media, including defined culture media, could be used to induce dermal fibroblast cells to produce their natural byproducts. (*e.g.*, *Faria Declaration*, ¶¶ 9, 11 and 13. Also, Specification page 11 line 25 to page 13 line 9, citing U.S. Patent No. 5,712,163, International PCT Publication No. WO 95/31473, a non-patent reference Ham and McKeehan, Methods in Enzymology, 58:44-93, 1979, Examples 4 and 15). *Second Faria Declaration,* ¶ 15.

Consequently, the culturing conditions to induce dermal fibroblast cells to produce their natural byproducts are all well known and are also disclosed in the Specification as filed (*e.g.*, Specification, page 12, line 10 to page 19 line 6, Examples 1 and 3). *Second Faria Declaration*, ¶ 16.

As was also previously explained, it is also well known what culture media could be used to form an epidermal cell layer from keratinocyte cells. *Faria Declaration*, ¶¶ 12-13. Therefore, it is also well known in the art what culturing conditions can be used to form an epidermal cell layer from keratinocyte cells, which are naturally found in such epidermal cell layers and they are also disclosed in the Specification as filed. (*e.g.*, ¶ 12 of *Faria Declaration*, Specification page 19, line 18 to page 21 line 11, citing U.S. Patent Nos. 5,712,163, 5,536,656 and 5,374,515, Examples 2, 4, 12 and 16). *Second Faria Declaration*, ¶ 17.

4. <u>The Level Of One Of Ordinary Skill</u>

One of ordinary skill in the art would be a scientist with an undergraduate degree in cell biology and at least two years of post graduate research or work experience in the field of tissue constructs. In addition to knowing which culture media to use (*Faria Declaration,* ¶¶ 11-13), one of ordinary skill in the art in view of the disclosure of the invention in the instant Specification would also know the culturing conditions to prepare a layer of dermal fibroblast cells that produce an extracellular matrix having such natural byproducts such as type I and type III collagen, decorin, fibronectin, tenascin and glycosaminoglycans, etc. *Second Faria Declaration*, ¶ 10.

Furthermore, in addition to knowing which culture media to use (*Faria Declaration,* ¶¶ 11-13), one of ordinary skill in the art would further know the culturing conditions that lead to the formation of epidermis. *Second Faria Declaration*, ¶ 10.

5. The Level Of Predictability In The Art

As stated above, it is well known what culturing conditions may be used to grow a layer of dermal fibroblasts or epidermal cell layer to produce their natural byproducts. *Supra*, Wands Factor 3. It is also well known what culturing conditions may be used to obtain those layers. *Id*. Moreover, it is also well known in the art how to prepare chemically defined media. *Id*. As such, the state of the art is predictable in the culturing conditions for the preparation of the dermal fibroblast and epidermal cell layers in chemically defined media. *Second Faria Declaration*, ¶¶ 15-17.

6. The Amount Of Direction Provided

The present Specification provides a number of directions on how to prepare the tissue construct of the invention. For example, the Specification discloses the culturing conditions to grow and expand fibroblast cells (*e.g.*, Specification page 11, line 11, to page 14 line 8, page 14, line 16, to page 18 line 19 and Examples 1, 3, 5, 6, 9-11, 15, 17). *Second Faria Declaration,* ¶ 18.

The Specification also discloses the culturing conditions to prepare a layer of extracellular matrix from dermal fibroblast cells in the absence of exogenous matrix components. (*e.g.*, Specification, page 17, lines 7-28, page 18, line 7, to page 19 line 6, page 23, line 26, to page 24 line 6, Example 1, 3, 5, 6, 9-11, 15, 17 and figure 1). *Second Faria Declaration*, ¶ 19.

For example, the Specification teaches that the dermal fibroblast cells are suspended in either base or growth media and are seeded on the cell culture surface at a density between about $1x10^5$ cells/cm^2 to about $6.6x10^5$ cells/cm^2, more preferably between about $3x10^5$ cells/cm^2 to about $6.6x10^5$ cells/cm^2 and most preferably at about $6.6x10^5$ cells/cm^2 (cells per square centimeter area of the surface). The cells are cultured in growth medium to establish the culture to between about 80% to 100% confluence at which time they are chemically induced to upregulate the synthesis and secretion of extracellular matrix without the use of a synthetic mesh member. (*e.g.*, Specification, page 18, lines 11-17). *Second Faria Declaration*, ¶ 20.

The Specification also teaches that the cultures are maintained in an incubator to ensure sufficient environmental conditions of controlled temperature,

humidity and gas mixture. Preferred conditions are between about 34 ^{0}C to about 38 ^{0}C, more preferably 37± 1 ^{0}C with an atmosphere between about 5-10 ± 1% CO_2 and a relative humidity (Rh) between 80-90%. (*e.g.*, Specification page 17, lines 25-28, Examples 1, 3, 4, 5, 6, 7, 10 etc.). *Second Faria Declaration*, ¶ 21.

The Specification further teaches the culturing conditions to prepare a layer of epidermal cells applied on the cell-matrix construct. (*e.g.*, Specification, page 19, line 18 to page 21, line 11, Examples 2, 8, 12 and 16.) *Second Faria Declaration*, ¶ 22.

That is, keratinocyte cells are seeded onto the cells matrix construct and are then induced to differentiate to forma a multilayer epidermis. In other words, the keratinocyte cells are grown by seeding and culturing between about $4.5x10^3$ cells/cm^2 to about $5x10^5$ cells/cm^2 epithelial cells to the upwardly facing surface of the cell-matrix construct to form a multilayer cell construct. The constructs are then incubated for between about 60 to about 90 minutes at 37 ± 1 ^{0}C, 10% CO_2 to allow the cells to attach. (*e.g.*, Specification, page 19 line 18 to page 20, citing U.S. Patent Nos. 5,712,163 and 5,536,656 , Examples 2, 4, 8, 12, and 16). *Second Faria Declaration,* ¶ 23.

Thus, as set forth above, the Specification is enabling for the optimization of culturing conditions for inducing human fibroblasts to produce a layer of extracellular matrix in the absence of exogenous matrix components (*e.g.*, page 17, lines 7-24, page 18, 7-19, Examples 1, 3, 5, 6, 9, 10, 15, 17 and figure 1), and for growing epidermal cells to form the cultured skin constructs of the presently

claimed invention (*e.g.,* page 19, lines 18-25, citing U.S. Patent Nos. 5,712,163 and 5,536,656). *Second Faria Declaration*, ¶¶ 18-25.

Accordingly, the Specification provides ample guidance for practicing the claimed invention. *Faria Declaration*, ¶¶ 18-25.

7. The Existence Of Working Examples

The Specification provides a number of working examples to practice the claimed invention. The working examples include a variety of different culturing conditions which can be used (*e.g.*, Examples 1, 2, 3, 5, 6, 8, 9, 10, 12, 15, 16, and 17). *Second Faria Declaration*, ¶ 24.

8. The Quantity Of Experimentation Needed

The quantity of experimentation needed, if any, would not be undue. First, one of ordinary skill in the art with the prerequisite education and work experience would know how to practice the cell culturing conditions for which the state of technology is well known in the art. (Factors 3-5, *supra*). Second, the Specification discloses the culturing conditions to prepare a layer of extracellular matrix from dermal fibroblast cells (Factor 6, *supra*).

Third, the present Specification both discloses and further provides working examples of conditions for culturing human fibroblasts and for the formation of an epidermal layer. (Factors 6-7, *supra*). Therefore, for all of these reasons, one of ordinary skill in the art would be able to practice the claimed invention without undue experimentation. *Second Faria Declaration*, ¶¶ 10-27.

As such, for the reason set forth above, Applicants respectfully submit that since the present Specification provides a number of directions and working examples, the Specification is

enabling for the pending claims and request that the rejection of claims 31-71 under 35 U.S.C. § 112, ¶ 1 be reconsidered and withdrawn.

The Examiner's Wand Factor Analysis and Arguments Are Incorrect

Applicants respectfully submit that analysis/arguments by the Examiner are incorrect and merit the withdrawal of this rejection. For example, the Examiner argues that the invention as claimed fails to recite what are the culturing conditions, for example, culture media contents, growth factors, support structure etc. that lead to the synthesis of the claimed extracellular matrix components to support the growth and proliferation of the second layer of epithelial cells. (*e.g.*, *Office Action*, page 6).

Applicants submit that the Specification provides ample guidance on the culturing conditions that lead to the synthesis of the extracellular matrix components (*e.g.*, Specification page 17, lines 7-28, page 18, line 7, to page 19 line 6, page 23, line 26, to page 24 line 6, Example 1, 3, 5, 6, 9-11, 15, 17 and figure 1, Wands Factor 6, *supra*). *Second Faria Declaration*, ¶¶ 18-20 and 24-25.

Further, the Specification teaches the culturing conditions that lead to the formation of epidermis (*e.g.*, Specification, page 19, line 18 to page 21, line 11, Examples 2, 8, 12 and 16, Wands Factor 6, *supra*.). *Second Faria Declaration*, ¶¶ 22-25.

Thus, for the reason set forth above, the Specification provides ample guidance on the culturing conditions and on the type of media which can be used at each step during the development of the cultured skin construct as claimed. *Second Faria Declaration*, ¶¶ 18-25.

Further, the Examiner argues that in addition to the "culturing conditions," the claims fail to recite what encompasses the "chemically defined media." (*e.g.*, *Office Action*, page 6).

However, the test for enablement is that "a patent need not teach, and preferably omits, what is well known in the art," *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Circ. 1991). Accordingly, as set forth above, Applicants submit that the formulations of the defined culture media are well known in the art (*e.g.*, *Faria Declaration*, ¶¶ 9, 11 and 13, also Specification page 11 line 25 to page 13 line 9, citing U.S. Patent No. 5,712,163, International PCT Publication No. WO 95/31473, a non-patent reference Ham and McKeehan, Methods in Enzymology, 58:44-93, 1979, Examples 4 and 15). *Second Faria Declaration,* ¶ 15.

Finally, the Examiner argues that the assembly of the cells into tissue is a highly orchestrated series of events. (*e.g.*, *Office Action*, page 6). However, the fact that the assembly of the cells into the tissue comprises a series of events does not render the present Specification non-enabling if the Specification teaches one of ordinary skill in the art how to practice each "event" without undue experimentation. (Factors 6-8, *supra*). *Second Faria Declaration*, ¶ 25.

As such, for all the reasons set forth above, Applicants respectfully submit that the Specification is enabling for the pending claims and request that the rejections of claims 31-71 under 35 U.S.C. § 112, ¶ 1 be reconsidered and withdrawn.

In light of the foregoing, the application is now believed to be in proper condition for allowance and a Notice to that effect is respectfully requested. If this *37 C.F.R. § 1.114 Response To Office Action* does not otherwise result in the issue of such Notice, the Examiner is respectfully invited to contact the Applicants' undersigned counsel for an interview.

No extra fee is believed due. However, if any additional fees are necessary, the Director is hereby authorized to charge such fees or credit any overpayment to Deposit Account No. 50-0540.

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